Professional Information for Estrofem®

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Estrofem® 1 mg, film-coated tablets

Estrofem®, 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Estrofem® 1 mg:

Each red film-coated tablet contains: Estradiol hemihydrate equivalent to estradiol 1 mg.

Excipients with known effects:

Contains sugar: Each tablet contains 37,3 mg lactose monohydrate.

Estrofem®:

Each blue film-coated tablet contains: Estradiol hemihydrate equivalent to estradiol 2 mg.

Excipients with known effects:

Contains sugar: Each tablet contains 36,8 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Estrofem® 1 mg: Round, red, film-coated, biconvex tablets engraved with NOVO 282.

Diameter 6 mm.

Estrofem®: Round, blue, film-coated, biconvex tablets engraved with NOVO 280. Diameter 6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The preparation is indicated for the treatment of symptoms due to estrogen deficiency in hysterectomised patients.

Continuous treatment with Estrofem® for more than five years is not recommended.

Estrofem® therapy may be used as an adjunct in preventing estrogen deficiency related osteoporosis in postmenopausal women at high risk of future fractures, who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

Estrofem® is administered orally.

The first tablet may be taken at any time. Then continue by taking one tablet daily without interruption, preferably at the same time each day, until all the 28 tablets have been taken.

Start a new pack the day after the last tablet has been taken.

In women with amenorrhoea and not taking HRT, or women transferring from another estrogen only HRT product, treatment with Estrofem® may be started on any convenient day.

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next twelve hours.

Otherwise the missed tablet should be discarded and the patient is advised to continue with the next day's tablet.

Estrofem® used for the treatment of symptoms due to estrogen deficiency should be given in the lowest effective dose as long as symptoms persist.

It is thus recommended that treatment should begin with a lower strength preparation of estradiol. The effect can be evaluated after 2 – 3 months, and in the event of insufficient effect, a change to Estrofem® 2 mg should be prescribed.

4.3 Contraindications

- Not for use during pregnancy.
- Known history (personal and/or family) or suspected breast cancer.
- Known or suspected estrogen dependent malignant tumours such as endometrial cancer or other hormone dependent tumours.
- Undiagnosed genital bleeding.
- Active liver disease. Acute or chronic liver disease or history of liver disease where the liver function tests have failed to return to normal.
- Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions.
- Inherited thrombophilia or known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency).
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis (DVT), pulmonary embolism).
- Active or previous arterial thromboembolic disease (e.g. angina, myocardial infarction and stroke).
- Porphyria.
- Hypertension.
- Haemoglobinopathies.
- Untreated endometrial hyperplasia.
- Known hypersensitivity to estradiol or to any of the excipients of Estrofem® (see section 6.1).

- Patients with known inherited genetic mutations: BRCA1 and BRCA2 genes.
- Early menstrual periods (before the age of 12 years).
- History of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma *in situ*).
- Previous treatment using radiation therapy to the chest or breast.
- Previous exposure to diethylstilbestrol (DES).

4.4 Special warnings and precautions for use

Medical examination/follow-up

Before initiating or re-instituting Estrofem®, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examinations should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised of what changes in their breasts should be reported to their doctor or nurse. Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

For the treatment of post-menopausal symptoms, Estrofem® should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and Estrofem® should only be continued as long as the benefit outweighs the risk.

As the experience in treating women with a premature menopause (due to ovarian failure or surgery) is limited, the evidence regarding the risks associated with Estrofem® in the treatment of premature

menopause is also limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Prolonged replacement therapy with unopposed estrogens may cause overstimulation of the uterus and breasts, which eventually could give rise to pathological conditions.

Prolonged replacement therapy with unopposed estrogens in postmenopausal women has been associated with endometrial carcinoma.

Conditions which need supervision:

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Estrofem®, in particular (see section 4.3):

- Leiomyoma (uterine fibroids) or endometriosis.
- A history of, or risk factors for, thromboembolic disorders.
- Risk factors for estrogen dependent tumours, e.g. 1st degree heredity for breast cancer.
- Hypertension.
- Liver disorders (e.g. liver adenoma).
- Diabetes mellitus with or without vascular involvement.
- Cholelithiasis.
- Migraine or (severe) headache.
- Systemic lupus erythematosus.
- A history of endometrial hyperplasia.
- Epilepsy.
- Asthma.
- Otosclerosis.

Reasons for immediate withdrawal of therapy:

Estrofem® should be discontinued in case a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function.
- Significant increase in blood pressure.
- New onset of migraine-type headache.
- Pregnancy.

Endometrial hyperplasia

The risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen -only users varies from 2- to 12-fold greater compared with non-users, depending on the duration of treatment and estrogen dose. After stopping treatment risk may remain elevated for at least 10 years.

The addition of progestagen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.

For oral doses of estradiol more than 2 mg, the endometrial safety of added progestagens has not been studied.

Unopposed estrogen stimulation may lead to pre-malignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestagens to Estrofem® should be considered in women who have undergone hysterectomy because of endometriosis if they are known to have residual endometriosis.

Breakthrough bleeding and spotting may occur during the first months of treatment in women with intact uterus. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

The overall evidence shows an increased risk of breast cancer in women taking combined estrogen-progestagen or estrogen-only HRT that is dependent on the duration of taking HRT.

The Women's Health Initiative study (WHI) found no increase in the risk of breast cancer in hysterectomised women using estrogen-only HRT. Observational studies have mostly reported a small increase in the risk of having breast cancer diagnosed that is substantially lower than that found in users of estrogen-progestagen combinations.

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

Hormone replacement therapy, including Estrofem® contains estrogen which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing breast cancer in 55 575 women 40 – 59 years of age who used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for estrogen-progestagen than estrogen-only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for estrogen-progestagen preparations was 1,60 at 1 – 4 years and RR = 2,08 at 5 – 14 years, while that for estrogen-only preparations were 1,17 at 1 – 4 years and 1,33 at 5 – 14 years. There was no risk to develop breast cancer in women who started MHT at 60 years of age.

All women on Estrofem® should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. Mammography evaluations should be done based on patient age, risk factors, and prior mammogram results.

HRT, especially estrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism

HRT such as Estrofem® is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later. One randomised controlled trial and epidemiological studies found a two- to three-fold higher risk for users compared with non-users.

Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

Generally recognised risk factors for VTE include use of estrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m²), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

The risk of VTE may be increased with prolonged immobilisation, major trauma or major surgery. Scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping Estrofem® four to six weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at a young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects), Estrofem® is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of the use of Estrofem®.

If VTE develops after initiating therapy, Estrofem® should be discontinued. Patients should be told to contact their doctors immediately when they are aware of potential thromboembolic symptoms (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use of estrogens and medroxyprogesterone and no overall benefit. For other HRT products such as Estrofem® there is only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality.

Stroke

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated estrogens (CEE) and medroxyprogesterone acetate (MPA).

The relative risk does not change with age or time since menopause.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies, including the WHI trial, suggest that use of combined HRTs may be associated with a similar or slightly smaller risk.

Depressed mood, depression and risk of suicidality

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Other conditions

Estrogen increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulins (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-l-antitrypsin and ceruloplasmin).

There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or Estrofem®.

Estrofem® may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Estrofem® is increased.

Women with pre-existing hypertriglyceridaemia should be followed closely during Estrofem® therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

Lactose monohydrate

Estrofem® contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take Estrofem®.

4.5 Interaction with other medicines and other forms of interaction

The metabolism of Estrofem® may be increased by concomitant use of substances known to induce medicine-metabolising enzymes, specifically cytochrome P450 enzymes such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine and efavirenz). Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's wort (*Hypericum perforatum*) may induce the metabolism of Estrofem®. Clinically, increased metabolism of Estrofem® may lead to decreased effect and changes in the uterine bleeding profile.

Effect of HRT with estrogens on other medicines

Hormone contraceptives containing estrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation.

This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicines together.

4.6 Fertility, pregnancy and lactation

Pregnancy

Estrofem® 1 mg is contraindicated during pregnancy. If pregnancy occurs during medication with Estrofem® 1 mg, treatment should be withdrawn immediately (see section 4.3).

Lactation

Estrofem® 1 mg is contraindicated during lactation.

4.7 Effects on ability to drive and use machines

Estrofem® has no known effect on the ability to drive or use machines.

4.8 Undesirable effects

Clinical experience:

The most frequently reported adverse reactions are breast tenderness/breast pain, abdominal pain, oedema and headache.

System Organ Class	Very common	Common	Uncommon	Rare
	≥ 1/10	≥ 1/100 < 1/10	≥ 1/1 000 < 1/100	≥ 1/10 000 <1/1 000

Psychiatric disorders		Depression		
Nervous system disorders		Headache		
Eye disorders			Abnormal vision (NOS - not otherwise specified)	
Vascular disorders			Venous thromboembolism (NOS - not otherwise specified)	
Gastrointestinal disorders		Abdominal pain or nausea	Dyspepsia, vomiting, flatulence or bloating	
Hepatobiliary disorders			Cholelithiasis	
Skin and subcutaneous tissue disorders			Rash or urticaria	
Musculoskeletal and connective tissue disorders		Leg cramps		
Reproductive system and breast disorders		Breast tenderness, breast enlargement or breast pain		

General disorders and administration site conditions		Oedema		
Investigations		Increased body mass		

Endometrial cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed estrogens such as Estrofem®. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1 000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and estrogen dose, the reported increase in endometrial cancer risk among unopposed estrogen users varies from 2- to 12-fold greater compared with non-users. Adding a progestagen to estrogen-only therapy greatly reduces this increased risk.

Ovarian cancer risk

Use of estrogen-only or combined estrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).
A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1,43, 95 % CI 1,31 – 1,56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2 000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2 000 will be diagnosed with ovarian cancer over a 5-year period.

Post-marketing experience:

In addition to the above-mentioned adverse reactions, those presented below have been spontaneously reported, (cannot be estimated from the available data).

- Immune system disorders: Generalised hypersensitivity reactions (e.g. anaphylactic reaction/shock).
- Nervous system disorders: Deterioration of migraine, stroke, dizziness, depression.
- Gastrointestinal disorder: Diarrhoea.
- Skin and subcutaneous tissue disorders: Alopecia.
- Reproductive system and breast disorders: Irregular vaginal
- bleeding in non-hysterectomised woman.
- Investigations: Increased blood pressure.

The following adverse reactions have been reported in association with other estrogen treatment:

- Myocardial infarction, congestive heart disease.
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism.
- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura, pruritus.
- Vaginal candidiasis.
- Estrogen -dependent neoplasms benign and malignant e.g. endometrial cancer, endometrial hyperplasia or increase in size of uterine fibroids in non-hysterectomised woman.
- Insomnia.
- Epilepsy.
- Libido disorder NOS (not otherwise specified).
- Deterioration of asthma.
- Probable dementia.
- Severe depression with a higher risk of suicidal thoughts/behaviour and suicide.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of Estrofem® is important. It allows continued monitoring of the benefit/risk balance of Estrofem®. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Estrofem® causes side effects which are related to its estrogenic and general metabolic effects. Overdosage may cause undesirable proliferation of the uterus, sodium and water retention, enlargement of the breasts, headache, dizziness, nausea and vomiting.

Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.21.8.1 Oestrogens.

Pharmacotherapeutic group: Natural and semisynthetic oestrogens, plain.

ATC code: G03CA03.

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of estrogen production in menopausal women.

Estrogens reduce bone loss following menopause or ovariectomy.

Estrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of estrogens on the bone mineral density is dose-dependent and appears to be effective as long as treatment is continued. After discontinuation of estrogen, bone mass is lost at a rate similar to that in untreated women.

5.2 Pharmacokinetic properties

Following oral administration of 17β-estradiol (E2) in micronised form, rapid absorption from the gastrointestinal tract occurs. It undergoes extensive first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 44 pg/mL (range 30 – 53 pg/mL) within 6 hours after intake of 2 mg.

The half-life of 17β-estradiol is about 18 hours. It circulates bound to SHBG (37 %) and to albumin (61 %), while only approximately 1 – 2 % is unbound. Metabolism of 17β-estradiol occurs mainly in the liver and the gut but also in target organs, and involves the formation of less active or inactive metabolites, including estrone, catecholestrogens and several estrogen sulphates and glucuronides. Estrogens are excreted by the bile, where they are hydrolysed and reabsorbed (enterohepatic circulation), and mainly in urine in biologically inactive form.

5.3 Preclinical safety data

Acute toxicity of estrogens is low. Because of marked differences between animal species and between animals and humans preclinical results possess a limited predictive value for the application of estrogens in humans.

In experimental animals estradiol or estradiol valerate displayed an embryolethal effect already at relatively low doses; malformations of the urogenital tract and feminisation of male fetuses were observed.

Preclinical data based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential revealed no particular human risks beyond those discussed in other sections of the professional information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose (E463)

Hypromellose

Lactose monohydrate

Magnesium stearate (E572)

Maize starch

Talc (E553b)

Titanium dioxide (E171).

Estrofem® 1 mg:

Red iron oxide (E172)

Propylene glycol (E1520).

Estrofem®:

Indigo carmine (E132)

Macrogol 400.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Do not refrigerate.

Keep the container in the outer carton until required for use.

Do not use after the expiration date marked on the label of the calendar dial pack and/or carton.

6.5 Nature and contents of container

Estrofem® is supplied in a calendar dial pack each containing 28 tablets.

The calendar dial pack with 28 tablets consists of the following 3 parts:

- The base made of coloured non-transparent polypropylene.
- The ring-shaped lid made of transparent polystyrene.
- The centre-dial made of coloured non-transparent polystyrene.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

90 Grayston Drive

Sandown

Sandton

Gauteng

2031

011 202 0500

8. REGISTRATION NUMBERS

Estrofem® 1 mg: 34/21.8.1/0159

Estrofem®: J/21.8.1/214

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Estrofem® 1 mg: 08 October 2001

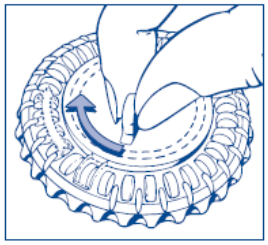
Estrofem®: 27 August 1979.

10. DATE OF REVISION OF THE TEXT

Date of revision: 17 February 2025

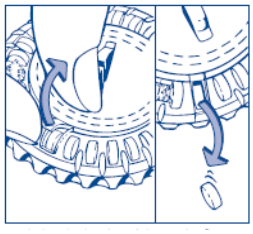
Instructions for use of the calendar dial pack

1. Set the day reminder:



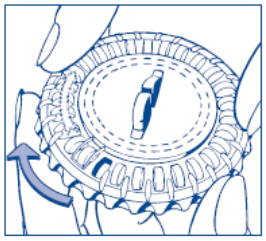
Turn the inner disc to set the selected day of the week opposite the little plastic tab.

2. How to take the first tablet:



Break the plastic tab and tip out the first tablet.

3. Every day:



Simply move the transparent dial clockwise one space as indicated by the arrow.

Tip out the next tablet.

The transparent dial can only be turned after the tablet in the opening has been removed.